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neo-Clerodane Diterpenoids from *Scutellaria altissima*

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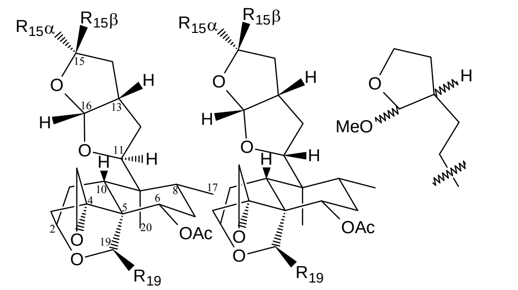
Nine *neo*-clerodane diterpenoids, scutaltisins B-G, scupolin I, scutecolumnin C and 11-*epi*-scutecolumnin C have been isolated from the acetone extract of the aerial parts of *Scutellaria altissima.* Scutaltisins B-G are new compounds, whereas scupolin I, scutecolumnin C and 11-*epi*-scutecolumnin C are reported in this species for the first time.

Keywords: *Scutellaria altissima*, Labiatae, *neo*-clerodane diterpenes, Scutaltisins.

The genus *Scutellaria* (Labiatae) has been extensively studied after it was proved a rich source of *neo*-clerodane diterpenes. These compounds aroused interest because of their biological activities [1-6] and potent insect antifeedant and antifungal compounds have been isolated from *Scutellaria* species [7-15]. Scutaltisin (now referred to as scutaltisin A, a 1:1 mixture of the C-15 epimers of 15-hydroxyscutecolumnin C), was previously reported as a new *neo*-clerodane diterpene from *S. altissima* [16]. The same compound was also isolated from *S. albida* [17] and named scutalbin C. Scutalsin (a 1:1 mixture of scutaltisin 19-*O*-2-methylpropanoyl ester) has been reported also from *S. altissima* [17] as the sole detectable diterpene constituent (Figure 1). Here, we report our results of a reinvestigation of the acetone extract of the aerial parts of *S. altissima,* showing the presence of a more complex cocktail of diterpenes. Nine *neo*-clerodanes were isolated and their structures elucidated: scutaltisins B-G (six new compounds), scupolin I, scutecolumnin C and 11-*epi*-scutecolumnin C (reported in this species for the first time).

Two TLC-homogeneous fractions (B1 and B2, see Experimental) were isolated from the acetone extract. The ^{1}H NMR spectum of B1 displayed the presence of some duplicate distinct signals [δ 5.54 and 5.63 (d, H-16); 2.008 and 2.010 (s, AcO)], and pointed out the presence of a close to 1:1 mixture of two major *neo*-clerodane derivatives, along with other minor components. The ^{1}H NMR spectral features of B1 and those reported for "an inseparable 3:7 mixture of scutecolumnin C and its C-11 epimer (11-*epi*-scutecolumnin C)", isolated from *S. columnae* var. *columnae* [18], supported a very close relationship. The additional presence of methoxy groups (δ 3.487 and 3.494) and the chemical shift of H-19



11*S* **11*R*** **6** scutaltisin G (R_{19}=OH)

R19	R15β	R15α	11*S*	11*R*
HO	H	H	scutecolumnin C	11-*epi*-scutecolumnin C
MeO	H	H	**2** scutaltisin C	**1** scutaltisin B
HO	H,OH (15*R*+15*S*)		scutaltisin A/scutalbin C	
MePrO	H,OH (15*R*+15*S*)		scutalsin	
MeO	H,OH (15*R*+15*S*)		**3** scutaltisin D	
HO	MeO	H	**4** scutaltisin E	
HO	H	MeO	**5** scutaltisin F	
MeO	MeO	H	scupolin I	

Figure 1: Structures of isolated *neo* clerodanes and compounds used in the discussion

(δ 5.097 and 5.123, *vs.* 5.72 and 5.74 of the parent structures, were similar to the reported values for 19-*O*-methyl ether derivatives such as scupolins H and I, both 5.11 [19]), completed the assignment of B1 as a mixture of 19-*O*-methyl ethers of scutecolumnin C and 11-*epi*-scutecolumnin C (**1** and **2**, respectively). Since MeOH was not used in the extraction-isolation procedure, formation of B1 as an artifact was excluded. One broad and a minor tail peak (rt 16.05 and 18.45 min) were observed in

Josep Coll was born in Barcelona (Feb. 19th, 1943). He obtained BSc and PhD degrees in Science (Licenciado and Doctor, Facultad de Ciencias, Sección Químicas) in 1964 and 1968 at the University of Barcelona. He became a research staff member of CSIC in 1968 (Colaborador Científico), and was promoted in 1970 and 1985 (to Investigador Científico and Profesor de Investigación, respectively). He worked as a postdoctoral fellow at UNB (Fredericton, NB, Canada) in 1970 and 1971 with Professors John A. Findlay (synthesis of insect juvenile hormones analogues) and Denny Valenta (synthetic approach to galanthamine). Back in Barcelona, early research was focused on synthesis of biologicaly active natural products, especially in the fields of mono- and sesquiterpenoids, and other substances related to the chemistry of insects (such as pheromones or insect attractants). Later on, the major subjects dealt with the isolation and structural elucidation of bioactive secondary metabolites from plant sources, mainly ecdysteroids (as insect moulting hormone analogues) and clerodane diterpenes (as antifeedants), along with a variety of related topics through cooperative international projects.
He has been an Advisory Board Member since the launching of NPC.

Table 1: ^{13}C NMR data of scutaltisins B/C and D **(1/2** and **3)** epimeric mixtures and reference compounds[a].

C	*mult*	**11*R*** R_{19}=OH[b]	**11*S*** R_{19}=OH[c]	R_{19}=OMe[d]	**1/2**	**15*R*+15*S*** R_{19}=OH[e,f]	**3**
1	CH_2	28.7	28.8	28.9	28.8/28.4	29.2/29.3	28.9
2	CH	66.5	66.8	66.7	66.7/66.5	67.0	66.70/66.74
3	CH_2	36.5	36.7	37.0	36.9/36.8	37.4	36.92/36.95
4	C	60.6	60.8	60.7	60.75/60.61	61.5	60.78/60.75
5	C	42.4[g]	42.5	42.7	42.65/42.67	43.6	42.68/42.69
6	CH	69.7	69.9	68.3	68.24/68.20	69.5/69.7	68.2/68.3
7	CH_2	31.1	32.7[h]	33.6	33.38/33.55	33.7	33.50/33.54
7[i]	***CH₂***	***33.4***	***33.5***				
8	CH	34.5	35.0	35.4	35.2/34.4	35.8	35.4/35.6
9	C	41.4[g]	41.4	41.0	42.47/41.67	41.4	41.1/41.0
10	CH	41.2	40.4	41.1	40.9/41.4	41.6	41.0/40.7
11	CH	83.4	85.9	84.2	86.13/83.85	84.5/85.0	84.5/84.8
12	CH_2	32.2	32.9[h]	33.5	34.2/32.4	33.4/34.0	32.90/33.48
13	CH	42.5	41.8	40.2	41.85/42.19	40.8/41.4	39.75/41.10
14	CH_2	33.4	33.5[h]	39.6	32.6/31.0	39.9/40.7	38.8/39.9
14[i]	***CH₂***	***31.1***	***32.7***				
15	CH_2	66.1	68.3		68.24/66.15		
15	CH			104.7		99.3/98.7	98.7/98.4
16	CH	107.7	108.3	109.7	108.2/107.8	108.7/109.9	107.9/110.0
17	CH_3	17.3	16.8	16.7	16.75/17.60	16.9	16.66/16.71
18	CH_2	49.6	49.7	49.8	49.9/49.8	49.5	49.8/49.9
19	CH	93.0	93.1	100.3	100.2/100.1	93.0	100.2/100.3
20	CH_3	12.2	13.9	13.9	14.0/12.3	14.2/14.3	14.0/14.1
Me***C***O	C	169.1	169.3	170.4	170.44/170.46	169.7	170.45
MeCO	CH_3	21.3	21.4	21.2	21.3	21.5	21.26/21.28
15-OMe	CH_3			54.5			
19-OMe	CH_3			55.2	55.27/55.33		55.3

[a] Lit. data for reference compounds are included for direct comparison; [b] 11-*epi*-scutecolumnin C [18]; [c] scutecolumnin C [20]; [d] scupolin I [19]; [e] scutaltisin [21]; [f] in pyridine d5; [g,h] these assignments may be interchanged; [i] bold italics for reassignment proposal.

analytical RP-HPLC with ELS detection (Supplementary data). NMR analysis of fractions collected in the range 14-17 min in the HPLC preparative system revealed a partial separation of the two compounds [named as scutaltisins B (**1**) and C (**2**), **1** moving faster] from other minor constituents and allowing separated spectral assignment, whereas the tail peak was identified as scupolin I [19].

Again MeO and distinct duplicate signals as above were observed in the NMR spectra of B2. Moreover, the signals were closely related to those reported for scutaltisin [16]. The presence of a C-15 epimeric mixture of scutaltisin 19-*O*-methyl ether was concluded, based on the major observed differences displayed by the H-19 hemiacetalic proton as above (δ 5.101 and 5.112 *vs.* 5.72 and 5.73 [16], or 5.71 and 5.70 [17]), and two MeO signals (δ 3.494,3.496). Whereas a shouldered peak was observed in analytical RP-HPLC with ELS detection (Supplementary data), the ^{1}H NMR spectrum revealed only traces of minor impurities. Preparative HPLC provided the pure mixture of **3** (scutaltisin D). Scupolin H [19], a prospective tetrahydrofurofuran precursor of **3** was not detected in the mixture.

The mother liquor of B2 crystallization provided a mixture of diterpenes (B2r1) displaying five major peaks on HPLC analysis (Supplementary data). Preparative HPLC yielded a partial separation of 11-*epi*-scutecolumnin C and scutecolumnin C from the first one. From the second and third peaks two further new compounds were isolated, namely 15β-methoxyscutecolumnin C (scutaltisin E, **4**) and 15α-methoxyscutecolumnin C (scutaltisin F, **5**), respectively, based on ^{1}H NMR data and comparison with reported values and the established rules for assigning the correct configuration at C-15 of 15-methoxyhexahydrofurofuran neoclerodane diterpenoids [22-26]. Although MeOH was used in the TLC/HPLC procedures, formation of **4** and **5** as artifacts from the precursor tetrahydrofurofuran scutalbin A (not detected in the mixture) was excluded since no change in chromatographic behavior was noticed. ^{1}H NMR data of the fourth peak displayed the presence of two OMe and one OAc signals (δ 3.34, 3.49 and 2.06), a doublet assigned as H-16 (δ 4.64, J = 1.8 Hz) and a particular H_2-15 multiplicity pattern (H-15$_A$: *δ* 3.86, *td* ; H-15$_B$: *δ* 3.93, *td*), pointing out a mixed structure **6** (named scutaltisin G) derived from scutaltisin A decalin core [H-2β (δ 4.24 m vs. 4.16), H-3α (δ 2.62 dt, vs. 2.52), H-6β (δ 4.65 dd vs. 4.68), Me-17 (δ 0.847 d vs. 0.90/0.92), H_2-18 (δ 2.45 d and 2.96 d vs. 2.43 and 2.95), H-19α (δ 5.72 s vs. 5.72/5.73 [14] and the open side chain as reported for scuterepenosides A_1-A_4 [27]. The small value for the H-16 doublet coupling constant points out a likely *trans* relationship of both protons in the furan ring.

Experimental

Structural data: IR spectra were recorded on a Vertex 70 FT-IR spectrometer (Bruker Optics) from 4000 cm^{-1} to 450 cm^{-1} at resolution 4 cm^{-1} with 9 scans.^{1}H NMR (400.13 MHz) and ^{13}C NMR (100.61 MHz) spectra were recorded on a Mercury 400 spectrometer (Varian, Zug, Switzerland) in $CDCl_3$, under standard 1D and 2D conditions and pulse sequences. TMS was used as internal standard and $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in ppm and coupling constants (*J*) in Hertz. Analytical HPLC work was performed on an Alliance 2695 apparatus coupled with a 996 UV diode array detector (Waters Corporation, Milford, MA, USA) together with Polymer Laboratories PL-ELS 1000 evaporative light scattering (ELS) detector (Amherst, MA, USA). A water-methanol gradient solvent system was used starting at 50:50 and up to 20:80 in 30 min, then back to initial conditions in 5 min, and column re-equilibration for 5 min, on a GEMINI 4.6 × 250 mm 5μm C-18 110Å column (Phenomenex, Torrance, USA) at 0.70 mL/min flow. A GEMINI 19 × 250 mm 5μm C-18 110Å column (Phenomenex, Torrance, USA) was used for preparative HPLC at 12.0 mL/min flow, and the same gradient as above. Three fractions were collected every min (labeled as minA, minB or minC) on a Waters fraction collector III (Waters Corporation). A C18 guard column was coupled to protect the integrity of the columns, both analytical and semi-preparative. Solvents used for extraction and chromatographic procedures were HPLC grade (Merck, Darmstadt, Germany), and water used in mobile phase mixtures was Milli Q (Millipore R, Billerica, MA, USA). Silica gel 60 F_{254} aluminum sheets (Merck, Darmstadt, Germany) were used for TLC monitoring. New diterpenes were further injected in an ACQUITY UPLC® (Waters Corporation, Milford, MA) with a Q-Tof Premier™ mass spectrometer detector (Waters Corporation) in the range 50-1500 Da under positive- and negative-ionization conditions.

Plant material: Plant material was collected in June 2011, in Bachkovo, near Assenovgrad, Bulgaria and voucher specimens (n. 17494) are deposited in the Herbarium of the Higher Institute of Agriculture at Plovdiv, Bulgaria.

Extraction and isolation: Dried and finely powdered aerial parts of *Scutellaria altissima* L. (750 g) were extracted with Me_2CO (2 × 3 L) at room temperature for 1 week. After filtration, the solvent was evaporated to dryness under reduced pressure yielding a gum (11.4 g), which was dissolved in 50 % aq. Me_2CO (v/v, 100 mL). The soln. was cooled to 4^{o} C for 24 h and filtered. The filtrate was extracted with $CHCl_3$ (4 × 50 mL). The organic extract was dried with Na_2SO_4 and evaporated under vacuum (giving 3 g, of a bitter residue). This residue was chromatographed over a Si gel column (Merck N. 7734, deactivated with 10 % H_2O, w/w, 35 g) with a light petroleum—EtOAc solvent gradient (from 10:0 to 1:9) as eluent. The collected eluates were pooled into 5 fractions based on TLC results: A (100 mg), B (450 mg), C (400 mg), D (50 mg) and E (1.2 g). Fraction B was subjected to CC (10 g of Si gel, deactivated as above; 100 mL/fractions) with a light petroleum—EtOAc solvent gradient as eluent, yielding **B1** (**1+2**, 15 mg, eluting with light petroleum—EtOAc, 3:1), crude **B2** (10 flasks eluting with light petroleum—EtOAc, 2:1; (83 mg), and **B3** (flasks containing a very complex mixture of more polar compounds not further studied, 25 mg). Homogeneous on TLC, **B2** (**3**, 16 mg) was obtained on acetone recrystallization [first crystallization from acetone yielded 20 mg of crude solid and 59.5 mg of residue from the solvent (**B2r**)]. This recovered material was subjected to preparative TLC (Merck, 2 mm plates, CH_2Cl_2 /MeOH solvent in ratio 100:2 as eluent) to yield 2 mg **3**, 29.3 mg of **B2r1** mixture and 11.2 mg of **B2r2** mixture.

HPLC results: A broad band and a minor tail peak (rt 16.05 and 18.45 min) were observed by analytical RP-HPLC with ELS detection of B1. Fractions were collected in the range 14-17 min in the HPLC preparative system. Scutaltisin B (**1**) and scutaltisin C (**2**) were partially separated. The tail peak was identified as scupolin I (17A). A shouldered peak (rt 11.65 min) was observed in analytical RP-HPLC with ELS detection for B2. Preparative HPLC provided the pure mixture of C-15 epimers of scutaltisin D (**3**) in the range 9A-10B. B2r1 resulted in a well separated mixture (3 major and 2 minor peaks: rt 9.86, 11.55, 12.98, 17.44 and 19.20 min) in analytical RP-HPLC with ELS detection. On preparative HPLC the first band provided a partial separation (10B, 70:30; 10C, 40:60) of 11-*epi*-scutecolumnin C and scutecolumnin C, whereas 15β-methoxyscutecolumnin C (scutaltisin E, **4**) and 15α-methoxyscutecolumnin C (scutaltisin F, **5**) were isolated from the second (12A) and third (14A) peaks respectively. Scutaltisin G (**6**) was isolated from the fourth peak (18B). The fifth peak (20A) provided too little amount of a mixture preventing any further effort. The chromatograms are shown in the Supplementary data section.

Scutaltisin B (scutecolumnin C 19-*O*-methyl ether) (**1**)
IR (**1+2**) $\surd_{max}$ (KBr) cm^{-1}: 3061 (oxirane), 2969, 2899, 2868, 1724, 1495, 1468, 1453, 1425, 1373, 1358, 1336, 1262, 1226, 1206, 1103, 1085, 1068, 1057, 1041, 1020, 974, 954, 930, 907, 878, 862, 847, 818, 778, 728, 622, 604, 575, 535, 479.
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09 (m, 1H, H-2*β*), 2.53 (dt, 1H, *J* = 13.4 Hz, *J* = 2.4 Hz, H-3*α*), 4.60 (dd, 1H, *J* = 11.6 Hz, *J* = 4.4 Hz, H-6*β*), 4.07 (dd, 1H, *J* = 11.1 Hz, *J* = 5.7 Hz, H-11*α*), 2.83 (m, 1H, H-13*β*), 3.88 (m, 2H, H-15), 5.63 (d, 1H, *J* = 5.1 Hz, H-16), 0.90 (d, 3H, *J* = 6.2 Hz, H_3-17), 2.36 (d, 1H, *J* = 4.4 Hz, H-18_A), 2.94 (d, 1H, *J* = 4.5 Hz, H-18_B), 5.10 (s, 1H, H-19*α*), 1.09 (s, 3H, H_3-20), 3.49 (s, OMe), and 2.012 (s, OAc).

Scutaltisin C (11-*epi*-scutecolumnin C 19-*O*-methyl ether) (**2**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13 (dt, 1H, *J* = 4.9 Hz, *J* = 2.4 Hz, H-2*β*), 2.55 (dt, 1H, *J* = 13.4 Hz, *J* = 2.4 Hz, H-3*α*), 4.63 (dd, 1H, *J* = 12.1 Hz, *J* = 4.7 Hz, H-6*β*), 3.64 (dd, 1H, *J* = 11.8 Hz, *J* = 4.9 Hz, H-11*α*), 2.79 (m, 1H, H-13*α*), 3.97 (t, 1H, *J* = 8.3 Hz, H-15_B) and 3.80 (ddd, 1H, *J* = 13.4 Hz, *J* = 8.5 Hz, *J* = 4.8 Hz, H-15_A), 5.54 (d, 1H, *J* = 5.5 Hz, H-16), 1.05 (d, 3H, *J* = 6.5 Hz, H_3-17), 2.34 (d, 1H, *J* = 4.5 Hz, H-18_A), 2.94 (d, 1H, *J* = 4.5 Hz, H-18_B), 5.13 (s, 1H, H-19*α*), 1.06 (*s*, 3H, H_3-20), 3.50 (s, OMe), and 2.015 (s, OAc).

Scutaltisin D [(1:1) C-15 epimeric mixture of (15R,15S)-scutaltisin 19-*O*-methyl ether] (**3**)
IR $\surd_{max}$ (KBr) cm^{-1}: 3521, 3380 (OH), 2953, 2900, 1730, 1456, 1375, 1334, 1258, 1227, 1205, 1182, 1164, 1088, 1071, 1056, 1025, 977, 940, 910, 879, 784, 621, 508.
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.09 (m, 1H, w½ = 10 Hz, H-2*β*), 2.53 (dt, 1H, *J* = 14.2 Hz, *J* = 2.9 Hz, H-3*α*), 4.60 and 4.62 (partially overlapping dd, 2 × 0.5H, *J* = 8.7 Hz, *J* = 4.2 Hz, H-6*β*), 4.51 (dd, 0.5H, *J* = 10.8 Hz, *J* = 6.2 Hz, H-11 of the 15*S* form), 3.98 (dd, 0.5H, *J* = 11.7 Hz, *J* = 4.9 Hz, H-11 of the 15*R* form), 5.64 (br d, 0.5 H, *J* = 5.1 Hz, H-15 of the 15*S* form) and 5.53 (d, 0.5 H, *J* = 5.6 Hz, H-15 of the 15*R* form), 5.79 and 5.80 (both d, 0.5H each, *J* = 5.3 Hz, H-16), 0.90 and 0.91 (both d, 1.5H each, *J* = 6.3 Hz, H_3-17), 2.36 and 2.35 (both d, 0.5H each, *J* = 4.5 Hz, H-18_A), 2.94 and 2.95 (both d, 0.5H each, *J* = 4.5 Hz, H-18_B), 5.10 and 5.11 (both s, 0.5H each, H-19*α*), 1.08 and 1.10 (both s, 1.5H each, H_3-20), 3.494 and 3.492 (s, OMe), and 2.013 and 2.012 (s, OAc).

Scutaltisin E (15β-methoxyscutecolumnin C) (**4**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.17 (m, 1H, H-2*β*), 2.58 (dt, 1H, *J* = 14.3 Hz, *J* = 2.8 Hz, H-3*α*), 4.68 (dd, 1H, *J* = 11.3 Hz, *J* = 4.4 Hz, H-6*β*), 3.97 (dd, 1H, *J* = 11.4 Hz, *J* = 4.7 Hz, H-11*α*), 2.95 (m, 1H, H-13*β*), 5.11 (d, 1H, *J* = 5.1 Hz, H-15), 5.71 (d, 1H, *J* = 5.4 Hz, H-16), 0.91 (d, 3H, *J* = 6.7 Hz, H_3-17), 2.43 (*d*, 1H, *J* = 4.1 Hz, H-18_A), 2.94 (d, 1H, *J* = 4.1 Hz, H-18_B), 5.73 (*s*, 1H, H-19*α*), 1.10 (s, 3H, H_3-20), 3.33 (*s*, OMe), and 2.06 (*s*, OAc).
MS calcd. for $C_{23}H_{34}O_8Na$ 461.2151 $[M+Na]^+$; found 461.2135

Scutaltisin F (15α-methoxyscutecolumnin C) (**5**)
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 4.18 (*m*, 1H, H-2*β*), 2.59 (dt, 1H, *J* = 14.6 Hz, *J* = 2.8 Hz, H-3*α*), 4.69 (dd, 1H, *J* = 12.2 Hz, *J* = 4.8 Hz, H-6*β*), 4.28 (dd, 1H, *J* = 11.0 Hz, *J* = 6.5 Hz, H-11*α*), 2.77 (m, 1H, H-13*β*), 4.97 (d, 1H, *J* = 5.5 Hz, H-15), 5.80 (d, 1H, *J* = 5.4 Hz, H-16), 0.92 (*d*, 3H, *J* = 6.1 Hz, H_3-17), 2.44 (d, 1H, *J* = 4.1 Hz, H-18_A), 2.96 (d, 1H, *J* = 4.1 Hz, H-18_B), 5.74 (s, 1H, H-19*α*), 1.07 (s, 3H, H_3-20), 3.30 (s, OMe), and 2.06 (s, OAc).
MS calcd. for $C_{23}H_{34}O_8Na$ 461.2151 $[M+Na]^+$; found 461.2164

Scutaltisin G (**6**)
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.24 (m, 1H, H-2*β*), 2.62 (dt, 1H, *J* = 14.0 Hz, *J* = 2.8 Hz, H-3*α*), 4.65 (dd, 1H, *J* = 10.0 Hz, *J* = 5.8 Hz, H-6*β*), 3.86 *(td,* 1H, *J* = 8.2 Hz, *J* = 7.8 Hz, H-15_A), 3.93 (td, 1H, *J* = 8.2 Hz, *J* = 4.1 Hz, H-15_B), 4.64 (d, 1H, *J* = 1.8 Hz, H-16), 0.847 (d, 3H, *J* = 5.8 Hz, H_3-17), 2.45 (d, 1H, *J* = 4.1 Hz, H-18_A), 2.96 (d, 1H, *J* = 4.1 Hz, H-18_B), 5.72 (s, 1H, H-19*α*), 0.854 (s, 3H, H_3-20), 3.34 and 3.49 (both s, OMe), and 2.06 (s, OAc).

Supplementary data: HPLC profiles and ^{1}H NMR spectra (with enlarged detailed sections for multiplets) are included in a "Supplementary Data" section.

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